AD-A103 136 LETTERMAN ARMY INST OF RESEARCH SAN FRANCISCO CA F/G 6/5
PHYSIOLOGIC ASPECTS OF PORCINE HEMORRHAGE. III. HEART RATE AND --ETC(U)
JUL 81 J P HANNON, R S DIXON, P B JENNINGS
UNCLASSIFIED LAIR-95

13

INSTITUTE REPORT NO. 95

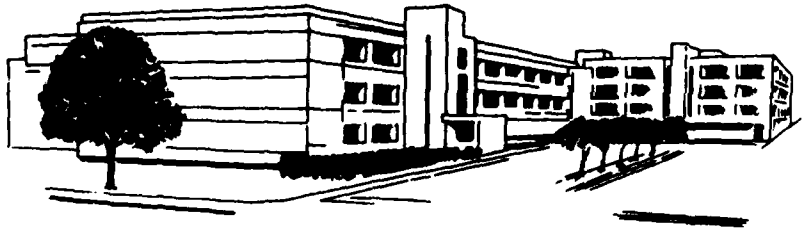
PHYSIOLOGIC ASPECTS OF PORCINE HEMORRHAGE

III. Heart Rate and Arterial Blood Pressure Changes during Spontaneous Recovery from 30 and 50 Percent Blood Volume Loss in the Conscious Animal

J. P. HANNON, PhD
P. B. JENNINGS, JR, VMD, LTC VC
and
R.S. DIXON, DVM, MAJ VC

DIVISION OF SURGERY
AND
DIVISION OF RESEARCH SUPPORT

JULY 1981



LETTERMAN ARMY INSTITUTE OF RESEARCH PRESIDIO OF SAN FRANCISCO CALIFORNIA 94129

Physiologic Aspects of Porcine Hemorrhage. III. Heart rate and arterial blood pressure changes during spontaneous recovery from 30 and 50 percent blood vlue loss in the conscious animal-- Hannon *et al*

In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

John L. Marshall J. K. July 87

(Signature and date)

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE	READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER: LAIR Institute Report No. 95	2. GOVT ACCESSION NO: AD-A103 136
4. TITLE (and Subtitle): Physiologic Aspects of Porcine Hemorrhage. III. Heart Rate and Arterial Blood Pressure Changes During Spontaneous Recovery from 30 and 50 Percent Blood Volume Loss in the Conscious Animal.	5. TYPE OF REPORT & PERIOD COVERED: Interim Jan-Dec 1980
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): J.P. Hannon, P.B. Jennings, Jr., VMD, LTC VC; R.S. Dixon, DVM, MAJ VC	8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Letterman Army Institute of Research, Divisions of Surgery and Research Support, Presidio of San Francisco, CA 94129	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: Proj No. 3S762772A814, Work Unit 091
11. CONTROLLING OFFICE NAME AND ADDRESS: U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD 21701	12. REPORT DATE: July 1981
	13. NUMBER OF PAGES: 27
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)	15. SECURITY CLASS. (of this report): UNCLASSIFIED
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

APPROVED FOR PUBLIC RELEASE; DISTRIBUTION IS UNLIMITED

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Hemorrhagic hypotension, swine spontaneous recovery, arterial pressure, heart rates

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Young domestic swine, six animals per group, were subjected to 30 and 50 percent hemorrhage of their estimated blood volume over a one-hour period while in a conscious recumbent state. Before and for five hours after hemorrhage, hemodynamic functions were measured to assess the characteristics of spontaneous recovery from hemorrhagic hypotension. Six additional pigs, treated similarly except for hemorrhage, served as controls. Immediately after 30 percent hemorrhage, arterial mean, systolic, and diastolic blood pressures were 79, 104, and

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

20. Abstract (Cont)

59 mm Hg, respectively. During the 5-hour recovery period, these pressures reverted to 105, 129, and 81 mm Hg, which were nearly the same as pre-hemorrhage values. Heart rates were unaltered by hemorrhage but increased slightly during recovery. Pulse pressure was not significantly affected by hemorrhage or recovery, while hematocrits declined during and following blood loss. After 50 percent hemorrhage, arterial mean, systolic, and diastolic pressures were 46, 79, and 26 mm Hg, respectively. During the recovery period these pressures rose 81, 104, and 62 mm Hg; all of these values remained significantly below pre-hemorrhage values. Pulse pressure increased significantly during the recovery period, while hematocrits decreased to an even greater degree than those in the 30 percent group. Heart rates were not significantly changed following 50 percent hemorrhage, but rose markedly during the first 4 hours of the recovery period. In both hemorrhage groups spontaneous recovery was associated with a progressive decrease in hematocrit which reflected a transfer of interstitial fluid to the circulation.

ABSTRACT

Young domestic swine, ~~six~~ animals per group, were subjected to 30 and 50 percent hemorrhage of their estimated blood volume over a ~~one-hour~~ period while in a conscious recumbent state. Before and for five hours after hemorrhage, hemodynamic functions were measured to assess the characteristics of spontaneous recovery from hemorrhagic hypotension. Six additional pigs, treated similarly except for hemorrhage, served as controls. Immediately after 30 percent hemorrhage, arterial mean, systolic, and diastolic blood pressures were 79, 104, and 59 mm Hg, respectively. During the 5-hour recovery period, these pressures reverted to 105, 129, and 81 mm Hg which were nearly the same as pre-hemorrhage values. Heart rates were unaltered by hemorrhage but increased slightly during recovery. Pulse pressure was not significantly affected by hemorrhage or recovery, while hematocrits declined during and following blood loss. After 50 ~~percent~~ hemorrhage, arterial mean, systolic, and diastolic pressures were 46, 79, and 26 mm Hg, respectively. During the recovery period these pressures rose to 81, 104, and 62 mm Hg; all of these values remained significantly below pre-hemorrhage values. Pulse pressure increased significantly during the recovery period, while hematocrits decreased to an even greater degree than those in the 30 ~~percent~~ group. Heart rates were not significantly changed following 50 percent hemorrhage, but rose markedly during the first 4 hours of the recovery period. In both hemorrhage groups spontaneous recovery was associated with a progressive decrease in hematocrit which reflected a transfer of interstitial fluid to the circulation.

PREFACE

This is the third in a series of reports on the physiological responses of the conscious domestic pig to severe hemorrhage. The first report dealt with chronic catheterization procedures, the second with heart rate and arterial pressure responses to 50 percent blood volume loss. The next report will be concerned with changes in blood gas and acid-base status during recovery from 30 and 50 percent blood volume loss.

We wish to express our appreciation for the conscientious and dedicated technical assistance provided by Marshall F. Jones, SFC; Maria V. De La Cerda, SSG; Robert J. Hughes, PFC; David Weber, SP4; and Nancy J. Champagne, SP4, in the surgical preparation of the animals, and Diane G. Arevalo for their care during all phases of the study. We also would like to thank Virginia L. Gildengorin, PhD, for the invaluable assistance she provided in developing the experimental design, statistical evaluation of acquired data, and preparation of graphic information. Lastly, we are highly indebted to Ann L. Wilkinson for the innumerable hours she spent in typing, proofreading, and assembling the manuscript, and to Lottie B. Applewhite for the many editorial and format improvements incorporated in this report.

TABLE OF CONTENTS

In a previous report (1), we described the heart rate and arterial pressure changes which occurred in young conscious pigs subjected to 50 percent hemorrhage of the estimated blood volumes. All eight of the animals used in that study showed signs and symptoms of shock during the latter stages of the bleeding procedure, including reduced arterial mean, systolic, and diastolic pressures, nausea, and in most instances, vomiting. Yet, subsequent to the bleeding procedures, all eight of the animals recovered spontaneously without replacement of the lost blood or other interventions. They were awake, alert, and hungry 24 hours later. In the present report, the heart rate, hematocrit, and arterial pressure changes associated with the first 5 hours of spontaneous recovery from 30 and 50 percent hemorrhage are described. Insofar as can be determined, all of these functional variables have not been studied previously in conscious swine.

METHODS

Eighteen young domestic swine, both barrows and gilts, were used in this study. They were obtained from a commercial hog farm (J.G. Boswell, Inc., P.O. Box 457, Corcoran, CA 93212) and were housed within an indoor laboratory facility for at least one week prior to experimental use. They were fed a commercial ration (Purina Pig Chow) and received water ad libitum.

At the time of experimental use, the pigs were distributed into three groups, each containing six individuals; one group served as controls, another was subjected to 30 percent hemorrhage, and the third was subjected to 50 percent hemorrhage. A chronic carotid artery catheter was implanted in each animal, as described previously (2), and 7 to 10 days were allowed for recovery from surgery. At the end of this time, each animal to be studied was fasted overnight and brought into the laboratory in a small mobile cage. Bedding material was provided, and after the animal voluntarily assumed a recumbent position

the carotid artery catheter was connected to a one-foot pressure monitoring/injection line (Cobe Laboratories, Inc.). The latter had been fitted previously with a three-way plastic stopcock (Pharmaseal, Inc.) and filled with heparinized saline (500 units/ml). Residual blood and heparinized saline were then aspirated from the catheter and the entire system was filled with fresh heparinized saline (10 units/ml). Thereafter, the stopcock was connected to a three-foot pressure monitoring/injection line (Cobe Laboratories, Inc.), previously filled with heparinized saline and this, in turn, was connected to a Statham P23 Db pressure transducer. The transducer was mounted to a ring stand and was positioned at heart level.

After at least 30 minutes of unrestrained recumbent rest, three sets of baseline control values for heart rate, systolic, diastolic, pulse, and integrated mean arterial pressure were obtained at ten-minute intervals. At these same points, a blood sample was removed for hematocrit determinations with a Clay-Adams microhematocrit centrifuge. The average control value for each variable was subsequently calculated; no statistically significant time-related change in any of these variables was noted during the control period.

Immediately after completion of the baseline control measurements, the bleeding procedure commenced in the pigs that were subjected to 30 or 50 percent hemorrhage. As previously described (1), total blood volume was estimated by the von Engelhardt regression equation (3); the relationship of blood volume to body weight dictated by this equation is illustrated in Figure 1.

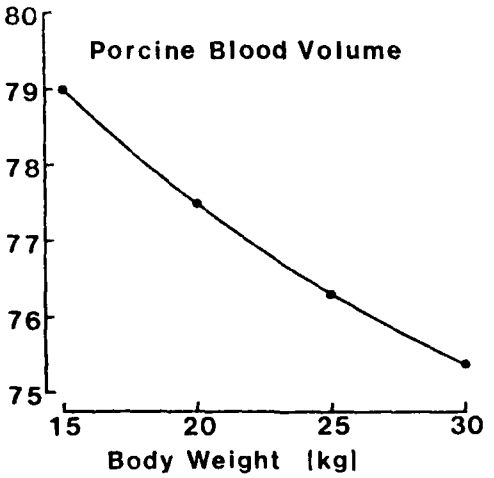


Figure 1. Blood volume of young domestic swine as estimated by the von Engelhardt regression equation. Ordinate in milliliters per kilogram.

The rate of blood removal in the hemorrhaged animals was gauged arbitrarily to an exponential scale such that 10 percent increments were removed uniformly from the pressure monitoring line with a 50 ml syringe over successive periods of 17, 20, and 23 minutes in the 30-percent hemorrhaged group, and over 9, 10, 11.5, 13.5, and 16 minutes in the 50-percent hemorrhaged group (Figure 2). In both groups, therefore, hemorrhage was completed in 60 minutes. Subsequent to the baseline control measurements, animals in the control group were maintained undisturbed for a period of one hour.

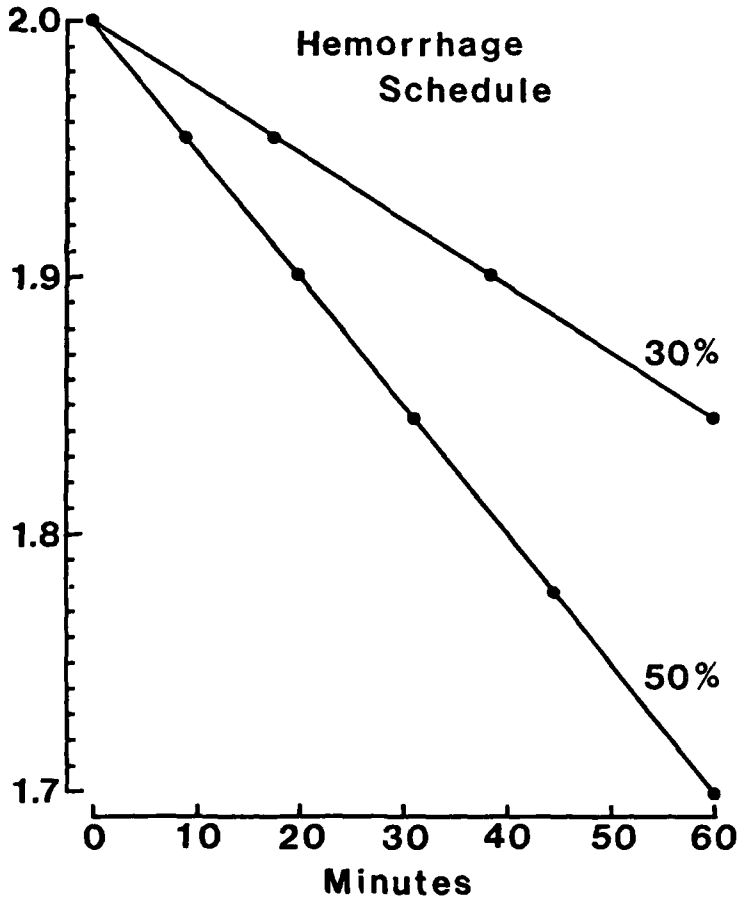


Figure 2. One-hour hemorrhage schedule for removal of 30 percent or 50 percent of the estimated blood volume. Ordinate in log percent of initial estimated blood volume.

Physiologic compensations, in terms of changes in hematocrit, heart rate, systolic, diastolic, and mean arterial pressure were followed over a 5-hour period subsequent to hemorrhage. Measurements were thus made at 0, 30, 60, 120, 180, 240, and 300 minutes post-hemorrhage. The control group of animals was similarly followed to assess the impact of potentially confounding diurnal changes in any of the measured variables. Recovery from hemorrhage, successful or not, was ascertained visually 24 hours after the hemorrhagic episode.

The data obtained from all three experimental groups were initially evaluated with two-factor analyses of variance. Subsequently, two-factor analyses of variance were applied to pairings of the experimental groups. Finally, single-factor analyses of variance were applied for the time variable. Statistical significance was assumed when $P \leq 0.05$.

RESULTS

Table 1 summarizes data on animal body weights, estimated blood volumes according to the von Engelhardt equation (3), and the blood volumes removed to achieve 30 and 50 percent hemorrhage. On the average, the hemorrhage groups had a lower body weight and, hence, tended to have somewhat smaller estimated blood volumes but higher relative volumes (per kg body weight) as compared to the control group. None of these differences, however, achieved statistical significance and, presumably, had no effect on the outcome of the various measurements.

During hemorrhage, all 6 pigs in the 50-percent group became nauseous and vomited shortly after blood loss exceeded 40 percent. These effects were not seen in any of the pigs in the 30-percent group. Whether nauseous or not, all of the hemorrhaged animals were distinctly lethargic and refractory to exogenous stimuli upon completion of the bleeding procedure, and these characteristics persisted throughout the 5-hour recovery period. All of the pigs survived the hemorrhage procedure and were alert 24 hours subsequently.

Table 2 summarizes the two-factor analyses of variance evaluations which were applied collectively to all three groups of animals. With two exceptions, the major effects and interactions for the experimental variables showed statistically significant ($P \leq 0.05$) effects. The exceptions were group heart rates which had a P value of 0.058 and pulse pressures which had a P value of 0.153.

Table 3 summarizes the two-factor analyses of variance evaluations which were applied to group pairs: control and 30-percent hemorrhage, control and 50-percent hemorrhage, and 30-percent and 50-percent hemorrhage. Again, a preponderance of the comparisons revealed significant main effects and interactions. These evaluations showed significant differences in group heart rates when animals subjected to 30- and

Table 1. Body weight, estimated blood volume, and hematocrit blood loss

Pig No.	Body Wt. (kg)	Blood Volume ml	Blood Volume ml/kg	Hemorrhage ml	Hemorrhage ml/kg
		Control			
12	20.5	1583	77.3		
19	20.9	1615	77.2		
25	25.0	1908	76.3		
30	29.1	2198	75.5		
32	25.5	1940	76.1		
35	28.2	2134	75.7		
Mean	24.3	1895	76.3		
SEM	±1.36	±1.04	±0.31		
		30% Hemorrhage			
18	20.0	1550	77.5	465	23.2
27	22.3	1713	76.8	514	23.0
28	24.5	1876	76.6	563	23.0
31	29.1	2198	75.5	659	22.6
34	25.9	1973	76.2	592	22.9
37	21.4	1648	77.0	494	23.1
Mean	23.9	1826	76.6	548	23.0
SEM	±1.36	± 97	±0.28	±29	±0.08
		50% Hemorrhage			
16	20.3	1580	77.8	790	38.9
21	20.5	1583	77.2	791	38.6
24	21.8	1680	77.1	840	38.5
29	28.2	2133	75.6	1067	37.8
36	22.7	1746	76.9	875	38.5
39	23.2	1778	76.6	889	38.5
Mean	22.8	1750	76.9	875	38.5
SEM	±1.18	±84	±0.30	42	±0.15

Table 2. Two factor analysis of variance summary: three groups

Measurement	F Ratio Group	Time	G x T
Heart rate	3.45	6.69*	2.95*
Hematocrit	10.06*	63.00*	15.79*
Mean arterial pressure	30.69*	42.53*	16.32*
Systolic pressure	28.96*	27.37*	10.35*
Diastolic pressure	28.92*	40.23*	18.18*
Pulse pressure	2.14	4.13	2.74*

*Indicates a significant ($P \leq 0.05$) effect: Groups, $F_{2,15} = 3.68$; Time, $F_{7,105} = 2.09$; G x T, $F_{14,105} = 1.78$.

Table 3. Two factor analyses of variance summary: group pairs

Measurement	Pair	F Ratio Group	Time	G x T
Heart rate	C x 30	0.01	2.06	2.77*
	C x 50	3.88	4.39*	4.81*
	30 x 50	6.38*	7.73*	1.46
Hematocrit	C x 30	12.91*	24.71*	22.32*
	C x 50	13.65*	19.71*	27.29*
	30 x 50	0.46	77.37*	1.45
Mean arterial pressure	C x 30	4.15	6.86*	10.66*
	C x 50	102.53*	44.31*	58.79*
	30 x 50	25.94*	53.51*	3.81*
Systolic pressure	C x 30	3.37	4.96*	8.52*
	C x 50	55.24*	22.18*	28.53*
	30 x 50	35.24*	31.78*	2.86*
Diastolic pressure	C x 30	5.41*	4.41*	8.21*
	C x 50	110.70*	48.35*	64.58*
	30 x 50	20.26*	54.48*	7.30*
Pulse pressure	C x 30	2.39	0.95	2.12*
	C x 50	3.86	3.70*	3.20*
	30 x 50	0.27	4.71*	2.57*

*Indicates a significant effect ($P \leq 0.05$): Group $F_{1,10} = 4.96$; Time, $F_{7,70} = 2.14$; G x T, $F_{7,70} = 2.14$.

50-percent hemorrhage were compared but, again, no significant between-group differences in pulse pressures were observed.

In view of the numerous group, time, and interaction effects that were statistically significant, the time factor for each experimental variable was evaluated with single-factor analysis of variance. The results of this evaluation are summarized in Table 4. The significant

Table 4. Single factor analysis of variance summary for time.

Measurement	Group	F Ratio
Heart rate	Control	0.77
	30% hemorrhage	3.07*
	50% hemorrhage	5.27*
Hematocrit	Control	1.72
	30% hemorrhage	38.37*
	50% hemorrhage	40.08*
Mean arterial pressure	Control	1.62
	30% hemorrhage	10.23*
	50% hemorrhage	81.00*
Systolic pressure	Control	1.89
	30% hemorrhage	7.82*
	50% hemorrhage	35.25*
Diastolic pressure	Control	1.86
	30% hemorrhage	7.61*
	50% hemorrhage	111.82*
Pulse pressure	Control	0.52
	30% hemorrhage	2.24
	50% hemorrhage	4.06*

*Indicates significant ($P \leq 0.05$) effect: $F_{7,35} = 2.29$.

time effects were limited to the two hemorrhage groups; no statistically significant changes were observed in the control group measurements. Only one measurement in the hemorrhaged pigs, pulse pressure

in the 30-percent group, failed to achieve statistical significance at $P \leq 0.05$, but even in this instance, the F ratio had a P value of 0.054.

Heart rate changes during and following hemorrhage are indicated in Figure 3. Both hemorrhage groups tended toward bradycardia, relative to control values, during the early stages of the recovery period.

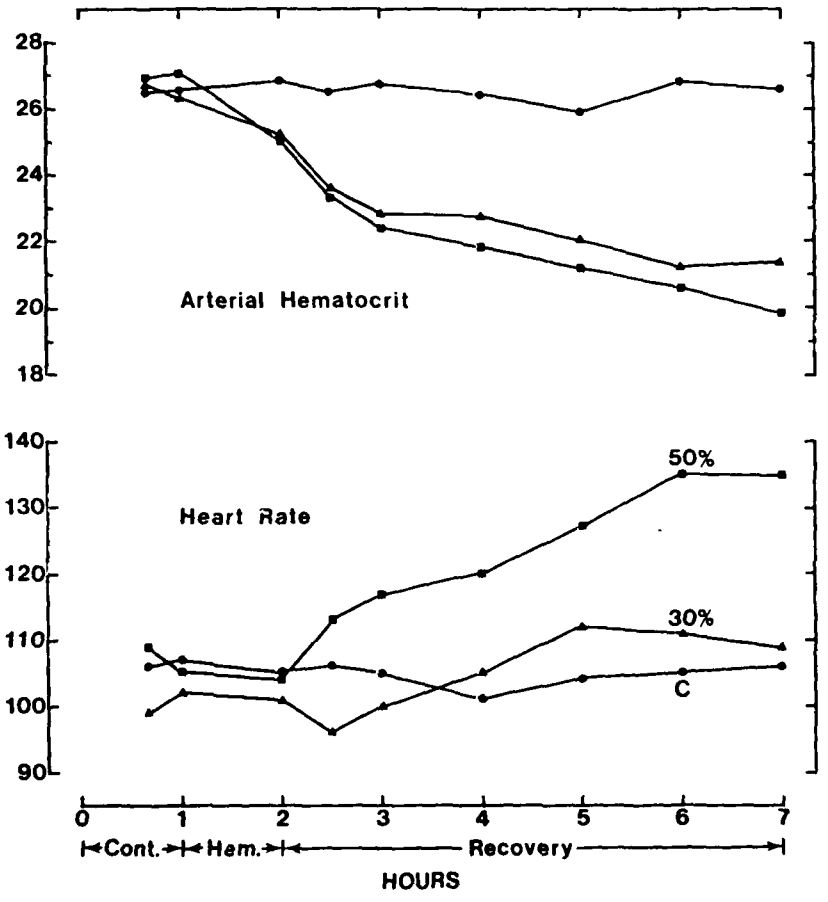


Figure 3. Effects of 30 percent and 50 percent blood volume loss on the arterial hematocrit and heart rates of conscious young domestic swine. C refers to control animals (N=6 pigs per group). Ordinate values in percent red cells (hematocrit)and mm Hg (heart rate).

These tendencies, however, were not statistically significant. As the recovery period progressed, progressive tachycardia was observed in the hemorrhaged animals, with the response being significantly more pronounced in the 50-percent group than in the 30-percent group. Plateau levels of tachycardia were reached at 180 minutes in the 50-percent group. The more pronounced response in the 50-percent group contributed to the significant time-x-group interaction indicated in Tables 2 and 3. The lack of significant change with time of the control group also contributed to this interaction.

Hematocrit decrements during the hemorrhage and recovery period are shown in Figure 3. Significant effects occurred in both the 30- and 50-percent groups during the bleeding episode itself, and these effects became progressively and significantly more pronounced during the recovery period. The changes were particularly marked over the first hour after hemorrhage, especially during the first 30 minutes. The total magnitude of the hematocrit decrement in the recovery period was surprisingly similar in the two hemorrhage groups. In fact, significant differences between the two groups were only seen at the latter stages. The statistically significant group-x-time interaction was attributable to the progressive hematocrit decrements in the hemorrhaged groups relative to the unchanged values in the control group.

The response characteristics of arterial mean, systolic, and diastolic pressures to 30 and 50 percent blood loss had a number of features in common (Figure 4): all three measurements showed a significant decrease as a result of the hemorrhage episode; all showed this decrement to be significantly more pronounced in the 50-percent than in the 30-percent group; all showed a significant, progressive increase during the recovery period, an effect that was responsible also for the highly significant interactions that were observed (Tables 2 and 3); and finally, all three showed at the end of the recovery period values that remained significantly depressed in the case of the 50-percent hemorrhage group, but no different from control values in the case of the 30-percent hemorrhage group. In terms of average values (± SEM), hemorrhage caused the mean arterial pressure to decrease from 115 ± 2.7 to 79 ± 7 mm Hg in the 30-percent group and from 105 ± 2.2 to 46 ± 3.5 mm Hg in the 50-percent group. During the same period, systolic pressure decreased from 134 ± 2.2 to 104 ± 5.9 mm Hg, and from 127 ± 2.2 to 79 ± 3.0 mm Hg in the 30- and 50-percent groups, respectively, while diastolic pressure decreased from 89 ± 2.1 to 59 ± 7.2 mm Hg and from 85 ± 2.2 to 26 ± 3.0 mm Hg. At the end of the 5-hour recovery period arterial mean, systolic, and diastolic pressures averaged, respectively, 105 ± 4.3 mm Hg, 129 ± 1.0 mm Hg, and 81 ± 4.0 mm Hg in the 30-percent group and 81 ± 1.8 mm Hg, 104 ± 2.1 mm Hg and 62 ± 1.6 mm Hg in the 50-percent group.

Pulse pressure (Figure 4) was not significantly altered (Table 3) by blood loss or recovery therefrom insofar as the 30-percent hemorrhage group was concerned. The 50-percent hemorrhage group, however,

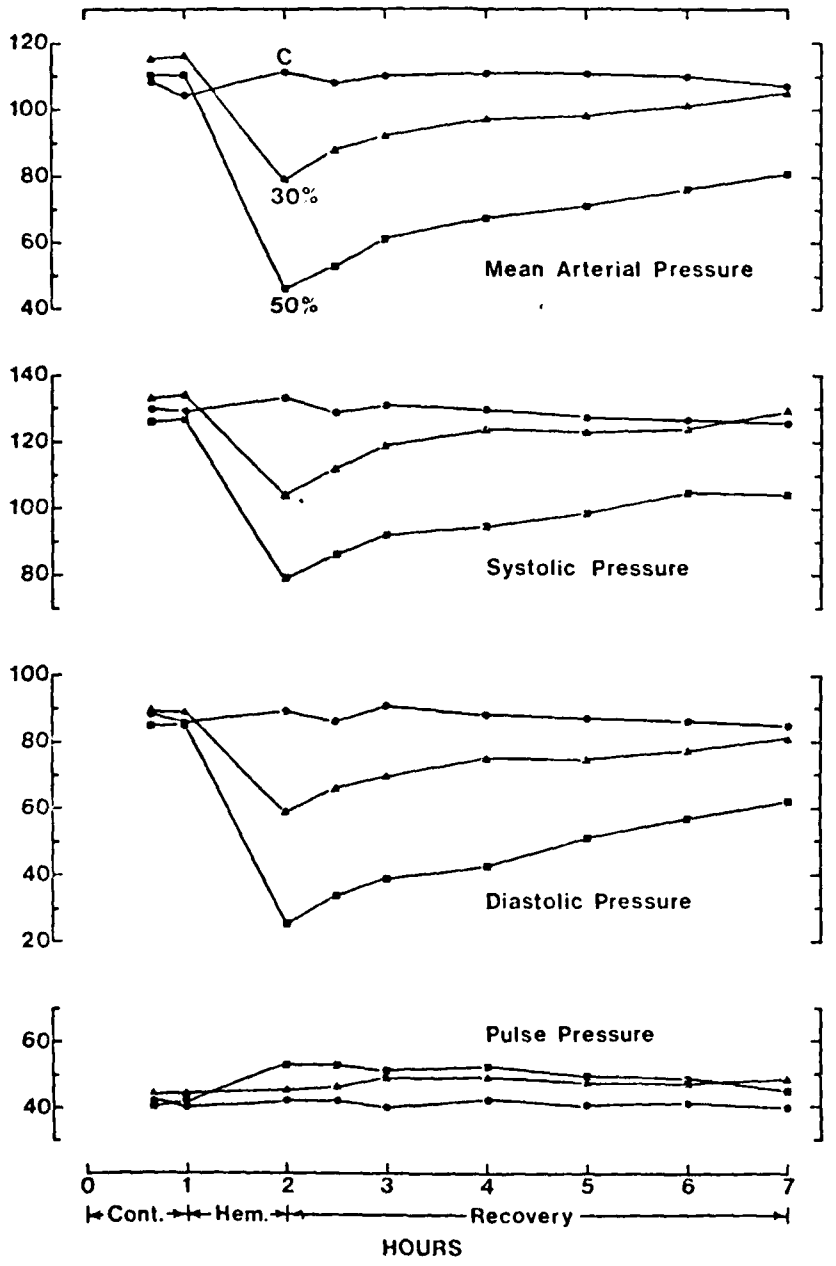


Figure 4. Effects of 30 percent and 50 percent blood loss on arterial mean, systolic, diastolic, and pulse pressures of conscious young domestic swine. C refers to control animals (N=6 pigs per group). Ordinate values in mm Hg.

showed a small but statistically significant elevation in pulse pressure following the bleeding episode, i.e., from 42 ± 2.3 to 53 ± 2.0 mm Hg. Subsequently, during the recovery period, pulse pressures in the group regressed toward control levels. This regression, relative to the unchanged values in the other two groups of animals, was responsible for the significant group-x-time interaction seen in Tables 2 and 3.

DISCUSSION

Although the domestic pig is becoming increasingly popular as an animal model for human-oriented investigations of hemorrhagic shock, relatively little is known about the hemodynamic compensations recruited by the pig during spontaneous recovery from severe blood loss. In humans, the capacity for spontaneous recovery may be of prime importance to post-hemorrhage survival when resuscitation is not readily available, for example, in a combat environment. Knowledge about this capacity, furthermore, may be of importance in the design of clinical treatment procedures. That swine can spontaneously recover from severe blood loss is readily attested by post-hemorrhagic studies of stress ulcer formation (4-9), gastric mucosal blood flow (10) and permeability (11,12), pulmonary function (13-15), liver enzymes (16), blood lactate concentration (17), and serum enzymes (18). Most porcine studies containing hemodynamic measurements have been conducted under anesthesia according to either of two procedures. In one, the animal is bled, usually rather rapidly, to a predetermined level of hypotension, and this level is maintained by further blood withdrawal or replacement for a predetermined time interval during which hemodynamic or other measurements are made (11,12,14,19,20). In the second procedure, the animal is similarly hemorrhaged, but at the end of the predetermined hypotensive period, all of the withdrawn blood is returned to the animal (13,15,16,18,21-23). The second procedure, it might be noted, was first developed by Wiggers (24) and his colleagues, and later improved by Lamson and De Turk (25). Neither of the procedures yields data that are directly comparable to the present study; first, because the use of anesthetics undoubtedly influenced their outcome (see (1) for references) and secondly, because the question of spontaneous recovery in the absence of experimental intervention was not addressed. Studies incorporating such procedures, nevertheless, have shown that hemorrhagic hypotension in swine is characterized by increased heart rate (16,18), reduced cardiac output (10-12,13,15,16,18, 20), little or no change in systemic vascular resistance (18), increased pulmonary vascular resistance (13,15), and reduced blood flow in the gastric mucosa (10,20), the hepatic artery and portal vein (22, 23). None of the foregoing reports, it should be emphasized, provide data on cardiovascular changes associated with the spontaneous recovery process.

One report that does contain such data is a study of anesthetized pigs by Hobler and Napodano (26) in which 10, 20, 30, or 40 percent

of the estimated blood volume was removed over a 30-minute period; total blood volume was assumed to be 6.5 percent of body weight, a value somewhat lower than that predicted by the von Engelhardt (3) equations for pigs of the size used in the study. Following hemorrhage, the pigs were left untreated in a so-called shock period for 2 hours, after which all of the hemorrhaged blood was returned to the circulation. During the shock period, mortality rates of 17, 66, 66, and 87 percent, respectively, were observed in the groups subjected to 10, 20, 30, and 40 percent hemorrhage. This observation, in contrast to the present study in which all animals survived, would seem to demonstrate the deleterious effects of anesthesia insofar as spontaneous recovery from hemorrhage is concerned. The surviving pigs in Hobler and Napodano's study (26), furthermore, showed a progressive decline in mean arterial pressure and a sustained depression of cardiac output. It was only with the reinfusion of lost blood that the functional variables improved.

Included among the few studies of conscious pigs, Simon and Olsen (27) measured mean arterial pressure immediately after removal of 10, 20, 30, and 40 percent of the estimated blood volume and, by means of the Sapirstein technique (28), blood flow to various tissues in separate groups of pigs 30 minutes after 20 and 40 percent blood volume loss. Simon and Olsen (27) also used a lower value for the estimated total blood volume than that based on the von Engelhardt equation (3). The changes they reported for mean arterial pressure, therefore, cannot be readily compared to those reported here, but it would appear that hemorrhage in Simon and Olsen's study (27) had a much more profound effect than that observed in the present investigation. Possible reasons for this divergence of results are also discussed elsewhere (1). In their measurements of tissue blood flow, Simon and Olsen (27) showed that 40 percent hemorrhage (equivalent to about 32 percent by the von Engelhardt equation) had no effect on the fractional distribution of the cardiac output to the lung, myocardium, kidney medulla, liver, small or large intestine, although absolute flow (unmeasured) was presumably reduced in proportion to the decrement in cardiac output (also unmeasured). Forty percent hemorrhage caused a 40 to 56 percent reduction in the fractional flow to the kidney cortex, various stomach tissues, skin and muscle, but a 108 percent increase in the fractional flow to the adrenals. In their 20-percent hemorrhage group (equivalent to about 16 percent by the von Engelhardt equation) only the stomach tissues showed a change in fractional flow, a 32 to 38 percent reduction. In companion papers, Simon and Olsen also demonstrated that the fractional distribution of cardiac output following hemorrhage was altered significantly by pentobarbital anesthesia (29) or by pretreatment with the vasopressor, metaraminol (30). None of the foregoing reports, unfortunately, were designed to characterize the progressive hemodynamic changes associated with spontaneous recovery from hemorrhagic hypotension.

Some data on spontaneous recovery in conscious swine are found in

the report of Orringer and Carey (17) who measured mean arterial pressures to 30-40 percent blood (exact hemorrhage time interval and amount were unspecified) one day after general anesthesia for surgical implantation of catheters. During hemorrhage, their animals showed a drop in mean pressure from 112 to 44 mm Hg. This change is comparable to that seen in the 50-percent hemorrhage group of the present study. Over a 90-minute spontaneous recovery, Orringer and Carey (17) recorded a slow increase in mean arterial pressure to 81 mm Hg, a value that was achieved after approximately 30 minutes in our 30-percent group and after 5 hours in our 50-percent group. The greater apparent post-hemorrhage decrement seen in Orringer and Carey's study (17) could have been due to more rapid blood loss or to a carry-over of anesthetic/surgical effects from catheter implantation to the hemorrhage and post-hemorrhage measurements.

To the best of our knowledge, the only other investigation involving hemodynamic measurements in conscious swine was contained in a study of myocardial glucose utilization reported by Stremple et al (31). These investigators, however, used pentobarbital anesthesia for the insertion of catheters, after which the animals were placed in a Pavlov sling and allowed 4 hours to recover from anesthesia before being subjected to 40-percent hemorrhage over a 10-minute period. Hemodynamic variables were measured before and for 40 minutes after hemorrhage. Treatments included post-hemorrhage infusions of 25 percent mannitol, 50 percent glucose, or 50 percent glucose with insulin. Measurements in their untreated (control) animals showed that the post-hemorrhage period was characterized by a decreased cardiac output, stroke volume, and mean arterial pressure, a decrease followed by an increase in total systemic resistance, and little, if any, change in heart rate. Two of the 6 animals contained in this group died before the 40-minute observation period was completed, and eventual mortality was 100 percent. Such mortality figures indicate that the hemorrhage procedure used by Stremple et al (31) was much more severe than that employed in the present study. At least three experimental varibles could account for this difference. Hemorrhage was conducted over a much briefer time interval in the study of Stremple et al (31) than in the present investigation, hence, their animals had far less opportunity to benefit from any compensatory responses that might have occurred during the bleeding period. The nature and impact of one of these compensations, transfer of interstitial fluid to the circulation, will be considered in a later section. A second variable would be the use of anesthesia 4 hours before hemorrhage, while a third would be the use of a Pavlov sling to physically restrain the animals during study. Thus, there could have been carryover effects of pentobarbital to the conscious state or emotional stress associated with physical restraint. Evidence that the second or third variable may have been operative is seen in the heart rate measurements reported by Stremple et al (31). Their pre-hemorrhage values averaged 169 beats per minute in one group of pigs and 176 in another group. Both of these averages are markedly higher than the mean pre-hemorrhage values (100 to 108 beats per minute) recorded in the present investigation.

As blood pressure is decreased following hemorrhage, interstitial fluid is transferred to the vasculature, thus compensating, at least in part, for the volume loss. This effect, as first described by Starling (32), occurs because plasma osmotic pressure exceeds capillary hydrostatic pressure. Starling (32) attributed the osmotic effect to plasma protein. Later investigators (33), however, showed that hemorrhage not only caused a decrease in arterial pressure but also caused an activation of sympathetic vasoconstrictor activity which reset the pre/postcapillary resistance ratio and further decreased the capillary hydrostatic pressure. In addition, hemorrhage-induced hyperglycemia has been shown (34) to cause an increase in plasma osmotic pressure which enhances fluid transfer to the circulation. These compensatory responses are activated well within the first hour after hemorrhage (34-36), and can markedly influence the degree of hemorrhage that can be tolerated without fatal consequences; the slower the rate of bleeding, the greater the amount of blood that can be lost (37,38).

The operation of these compensatory factors was clearly evident in the present investigation. During the one-hour hemorrhage period, the average hematocrit decreased from 26.5 to 25.2 in the 30-percent group and from 27.0 to 25.0 in the 50-percent group (Figure 1). Plasma glucose values increased 19.3 and 82.9 percent in the two groups, respectively (unpublished results).

Aside from accounting, at least in part, for the improved hemorrhage tolerance of the pigs used in the present study, relative to those used by Stremple et al (31), the hematocrit reduction during hemorrhage also indicated that the actual blood volume reduction was less than the 30 or 50 percent supposedly removed. Is it possible to estimate what the actual decrements were? At first approximation, if it is assumed that 30 percent or 50 percent of the circulating red cell volume was removed by hemorrhage and that hematocrit decrement is entirely due to an influx of interstitial fluid, then the amount of influx in relative terms can be calculated by rearrangement of the following equation:

$$Hct = \frac{RCV}{RCV + PV} \qquad (1)$$

Where Hct refers to hematocrit, RCV is circulating red cell volume and PV is plasma volume. Rearrangement to solve for plasma volume yields:

$$PV = \frac{RCV\ (1-Hct)}{Hct} \qquad (2)$$

Thus, if the initial blood volume (BV) of the 30-percent hemorrhage group is assigned a normalized value of 100 and the hematocrit, as measured, is 0.265, then the normalized RCV volume would be 26.5 and the normalized PV would be 73.5. Immediately after hemorrhage, RCV would be (0.7)(26.5) or 18.55, and upon inserting this value and a

measured hematocrit of 0.252 into equation 2, PV would be 55.06 while BV would be 18.55 plus 55.06 or 73.61. In short, this first approximation predicts that 26.4 percent, not 30 percent, of the initial BV was removed by the hemorrhagic procedure. Similar calculations with the 50-percent group would predict a BV reduction of 46 percent. Actually, these predicted decrements probably overestimate the true blood loss because during hemorrhage the influx of interstitial fluid dilutes the red cells, hence reduction in RCV would be less than the 30 or 50 percent assumed. If, therefore, it is further assumed that the dilution effect is similar for both plasma and red cells, then a second and presumably closer approximation of the post-hemorrhage RCV would be:

$$\frac{\text{Predicted PV}}{\text{Assumed PV}} \times \text{assumed RCV}$$

or for the 30 percent group:

$$\text{RCV} = \frac{55.06}{(73.5)(0.7)} \times (0.7)(26.5) = 19.85$$

Insertion of a rounded PV value of 19.9 into equation 2 would yield a revised post-hemorrhage PV of 59.1 and blood volume of 79.0. Similar estimate revisions for the 50-percent hemorrhage group yield a post-hemorrhage RCV value of 15.0, a PV of 45.0, and a BV of 60.0. These second estimates, therefore, would predict blood volume decrements of 21.0 percent and 40.0 percent, respectively, instead of 30 percent and 50 percent for the two groups of hemorrhaged pigs.

Equation 2 can also be used to predict the relative magnitude of interstitial fluid influx, hence the relative magnitude of the plasma volume and blood volume compensations during spontaneous recovery from hemorrhage. These predictions possess a greater degree of certainty since they are based on the relatively safe assumption that RCV does not change materially once the hemorrhage procedure is complete. If the foregoing estimates of PV, RCV, and BV are used as starting points, Table 5 summarizes the relative values that would appear for the 30-percent group over the course of the recovery period. A similar summary for the 50-percent group is contained in Table 6. It is obvious from both of these tables that spontaneous recovery from hemorrhage occurs quite rapidly and involves significant transfer of interstitial fluid to the circulation.

Table 5. Predicted normalized values for red cell volume, plasma volume, and blood volume during hemorrhage and recovery of swine subjected to an assumed 30% reduction in blood volume.

Time	Hct	RCV	PV	BV	Δ BV
Controls	0.265	16.5	73.5	100	0
0	0.252	19.9	59.1	17.0	21.0
30	0.236	19.9	64.4	84.3	15.7
60	0.228	19.9	67.4	87.3	12.7
120	0.227	19.9	67.8	87.7	12.3
180	0.220	19.9	70.6	90.5	9.5
240	0.212	19.9	74.0	93.9	6.1
300	0.213	19.9	73.5	93.4	6.6

The following abbreviations were used: HCT - hematocrit; RCV - red cell volum; PV - plasma volume, BV - blood volume.

Table 6. Predicted normalized values for red cell volume, plasma volume, and blood volume during hemorrhage and recovery of swine subjected to an assumed 50% reduction in blood volume.

Time	Hct	RCV	PV	BV	ΔBV
Controls	0.270	27.0	73.9	100	0
0	0.250	15.0	45.0	60.0	40.0
30	0.233	15.0	49.4	64.4	35.6
60	0.224	15.0	52.0	67.0	33.0
120	0.218	15.0	53.8	68.8	31.2
180	0.212	15.0	55.8	70.8	29.2
240	0.206	15.0	57.8	72.8	27.2
300	0.199	15.0	60.4	75.4	24.6

The following abbreviations were used: HCT - hematocrit; RCV - red cell volume; PV - plasma volume; BV - blood volume.

CONCLUSIONS

- As evidenced by 24-hour survival, conscious young domestic pigs can successfully compensate for 30 and 50 percent losses of estimated blood volume on the basis of the results reported in the literature, conscious animals have a far greater compensatory capacity than the anesthetized animals.

- Rapid transfer of fluid from the interstitial space to the vasculature constituted a major compensatory process. It replenishes blood volume and returns arterial pressures toward pre-hemorrhage values. Estimates of the magnitude of this transfer over a 5-hour post-hemorrhage period indicates nearly complete recovery in pigs subjected to 30-percent blood volume loss and about one-half recovery in pigs subjected to a 50-percent blood volume loss.

- In view of the similarities in human and porcine compensations to hemorrhage, it would appear likely that humans can successfully survive moderately severe blood loss without resuscitative intervention. If this can be firmly established, it would have a major impact on the management of certain combat casualties, i.e., those in which blood loss does not exceed limits compatible with spontaneous recovery.

RECOMMENDATIONS

- Spontaneous compensations of the conscious pig to severe hemorrhage should be described in terms of changes in blood gas and acid-base status, tissue blood flow, and kinetics of fluid transfer from the interstitial and intracellular space to the vasculature.

- Alterations in metabolic status as reflected by oxygen transport characteristics and blood chemical changes should be delineated during and following hemorrhage in the conscious pig.

- The critical physiological and biochemical factors leading to fatalities following massive hemorrhage to the conscious pig should be described.

REFERENCES

1. HANNON, J.P., P.B. JENNINGS, JR., and R.S. DIXON. Physiologic aspects of porcine hemorrhage. II. Alterations in heart rate and arterial pressure during fifty percent blood volume loss in the conscious animal. Report No. 94. San Francisco, California: Letterman Army Institute of Research, 1981

2. DIXON, R.S., P.B. JENNINGS, JR., and J.P. HANNON. Physiologic aspects of porcine hemorrhage. I. A vascular catheter for chronic implantation in swine. Report No. 93. San Francisco, California: Letterman Army Institute of Research, 1981

3. von ENGELHARDT, W. Swine cardiovascular research -- a review. In: Swine in Biomedical Research, edited by L.K. Bustad and R.O. McClellan. Seattle: Frayn Printing, 1966. pp 307-329

4. NORTON, L., P. NOLAN, J.E.L. SALES, and B. EISEMAN. A swine stress ulcer model. Ann Surg 176:133-138, 1972

5. COLLAN, Y., E. KIVILAAKSO, T.V. KALIMA, and M. LEMPINEN. Ultrastructural changes in the gastric mucosa following hemorrhage in shock. Circ Shock 4:13-25, 1977

6. VOITK, A.J., C-J. CHIU, and F.N. GURD. Prevention of porcine stress ulcer following hemorrhagic shock with an elemental diet. Arch Surg 105:473-476, 1972

7. HOTTENROTT, C., R.M. SEIFERT, and H. BECKER. The role of ischemia in the pathogenesis of stress induced gastric lesions in piglets. Surg Gynecol Obstet 146:217-220, 1978

8. BECKER, H., C. HOTTENROTT, R.M. SEIFERT, and L. VON GERSTENBERCK. Erfahrungen mit dem haemorrhagischen Schock beim Ferkel. Res Exp Med (Berlin) 170:125-131, 1977

9. GOODMAN, A.A., and M.P. OSBORNE. An experimental model and clinical definition of stress ulceration. Surg Gynecol Obstet 134: 563-571, 1972

10. LEVINE, B.A., W.H. SCHWESINGER, D. JONES, and K.R. SIRINEK. Histamine control of gastric microvasculature in shock. J Surg Res 26:532-539, 1979

11. TAYLOR, B.M., A.A. DRIEDGER, and D.P. GIRVAN. Effect of cimetidine on gastric mucosal permeability after hypovolemic shock using isotope assessment. Surg Forum 30:3-5, 1979

12. TAYLOR, B.M., B.D. REID, A.A. DRIEDGER, and D.P. GIRVAN. Radiotracer assessment of gastric mucosal permeability after hemorrhagic shock. Can J Surg 23:59-62, 1980

13. NOBLE, W.H. Early changes in lung water after hemorrhagic shock in pigs and dogs. Can Anesth Soc J 22:39-49, 1975

14. LOWERY, B.D., and J.M. SUGG. Pulmonary dysfunction after shock and trauma. Adv Exp Med Biol 23:415-435, 1971

15. BURGHUBER, O., B. BINDER, M. KOCH, I. LEHR, A. MITSCH, and M. WAGNER. Zur Frage des Verhaltens der Thrombozyten bei experimentellem Volumenmangelschock. Wein Klin Wschr 89:341-345, 1977

16. NAGASUE, N., P.E. FREDLUND, B. KALLUM, T. OLIN, and S. BENGMARK. Effect of glucocorticoids on release of lysosomal enzymes in liver ischemia and hemorrhagic shock in pigs. Jap J Surg 4:37-47, 1974

17. ORRINGER, R., and L.C. CAREY. A comparison of arterial and venous lactate levels in low flow states. Wisconsin Med J 72:254-256, 1973

18. FREDLUND, P.E., B. KALLUM, N. NAGASUE, T. OLIN, and S. BENGMARK. Release of acid hydrolases in hemorrhagic shock after pretreatment with hydrocortisone in the pig. Am J Surg 128:324-330, 1974

19. CAREY, L.C., and M. WALLACK. Blood sugar response to graded hemorrhage in the pig. Surg Forum 21:89-90, 1970

20. LEVINE, B.A., W.H. SCHWEISINGER, K.R. SIRINEK, D. JONES, and B.A. PRUITT. Cimetidine prevents reduction in gastric mucosal blood flow during shock. Surgery 84:113-119, 1978

21. FREDLAND, P.E., P.A. Ockerman, and J.O. VANG. Plasma activities of acid hydrolases in experimental oligemic shock. Am J Surg 124:300-305, 1972

22. LINDBERG, B., and N. DARLE. The effect of dextran 40 and blood transfusion on hepatic circulation and oxygen consumption in hemorrhagic shock. J Surg Res 23:264-273, 1977

23. LINDBERG, B., and N. DARLE. The effect of glucagon and blood transfusion on hepatic circulation and oxygen consumption in hemorrhagic shock. J Surg Res 23:557-563, 1977

24. WIGGERS, C.J. Physiology of Shock. New York: Commonwealth Fund, 1950

25. LAMSON, P.D., and W.E. De TURK. Studies on shock induced by hemorrhage. XI. A method for the accurate control of blood pressure. J Pharmacol Exp Therap 83:250-252, 1945

26. HOBLER, K.E., and R.J. NAPONDANO. Tolerance of swine to acute blood volume deficits. J Trauma 14:716-718, 1974

27. SIMON, M.A., and W.R. OLSEN. Capillary flow in hemorrhagic shock. I. Hemorrhage in the nonanesthetized pig. Arch Surg 99:631-633, 1969

28. SAPIRSTEIN, L.A. Regional blood flow by fraction distribution of indicators. Am J Physiol 193:161-168, 1958

29. SIMON, M.A., and W.R. OLSEN. Capillary flow in hemorrhagic shock. II. Hemorrhage in the anesthetized pig. Arch Surg 99:634-636, 1958

30. OLSEN, W.R. Capillary flow in hemorrhagic shock. III. Metaraminol and capillary flow in the nonanesthetized and anesthetized pig. Arch Surg 99:637-640, 1969

31. STREMPLE, J.F., H. THOMAS, V. SAKACH, and D. TRELKA. Myocardial utilization of hypertonic glucose during hemorrhagic shock. Surgery 80:4-12, 1976

32. STARLING, E.H. On the absorption of fluids from the connective tissue spaces. J Physiol (London) 18:312-326, 1896

33. MELLANDER, S. Comparative studies on the adrenergic neurohormal control of resistance and capacitance blood vessels in the cat. Acta Physiol Scand 50 (Suppl 176):1-84, 1975

34. JÄRHALT, J. Osmolar control of the circulation in hemorrhagic hypotension. Acta Physiol Scand 94 (Suppl. 423):1-84, 1975

35. HADDY, F.J., J.B. SCOTT, and J.I. MOLNAR. Mechanism of volume replacement and vascular constriction following hemorrhage. Am J Physiol 208:169-181, 1965

36. ÖBERG, B. Effects of cardiovascular reflexes on net capillary fluid transfer. Acta Physiol Scand 71:233-247, 1970

37. ELMAN, R., C. LISHER, and H.W. DAVEY. Red cell volume, plasma albumin and globulin level in fatal surgical shock due to repeated hemorrhage. Am J Physiol 140:737-741, 1943

38. SWINGLE, W.W., J.J. PFIFFNER, H.M. VARS, and W.M. PARKINS. The effect of hemorrhage on normal and adrenalectomized dog. Am J Physiol 107:259-274, 1934

OFFICIAL DISTRIBUTION LIST

Comander
US Army Medical Research and Development Command
ATTN: SGRD-SI/ Mrs. Madigan
Fort Detrick, Frederick MD 21701

Defense Technical Information Center
ATTN: DTIC-DDA (12 copies)
Cameron Station
Alexandria VA 22314

Director of Defense Research and Engineering
ATTN: Assistant Director, Environmental and Life Sciences
Washington DC 20301

The Surgeon General
ATTN: DASG-TLO
Washington DC 20314

HQ DA (DASG-ZXA)
WASH DC 20310

Superintendent
Academy of Health Sciences
ATTN: AHS-COM
Fort Sam Houston TX 78234

Assistant Dean
Institute and Research Support
Uniformed Services University of Health Sciences
6917 Arlington Road
Bethesda MD 20014

Commander
US Army Environmental Hygiene Agency
Aberdeen Proving Ground MD 21070

US Army Research Office
ATTN: Chemical and Biological Sciences Division
P.O. Box 1221
Research Triangle Park NC 27709

Biological Sciences Division
Office of Naval Research
Arlington VA 22217

Director of Life Sciences
USAF Office of Scientific Research (AFSC)
Bolling AFB
Washington DC 20332

Director
Walter Reed Army Institute of Research
Washington DC 20012

Commander
US Army Medical Research Institute of Infectious Diseases
Fort Detrick, Frederick MD 21701

Commander
US Army Research Institute of Environmental Medicine
Natick MA 01760

Commander
US Army Institute of Surgical Research
Brooke Army Medical Center
Fort Sam Houston TX 78234

Commander
US Army Institute of Dental Research
Washington DC 20012

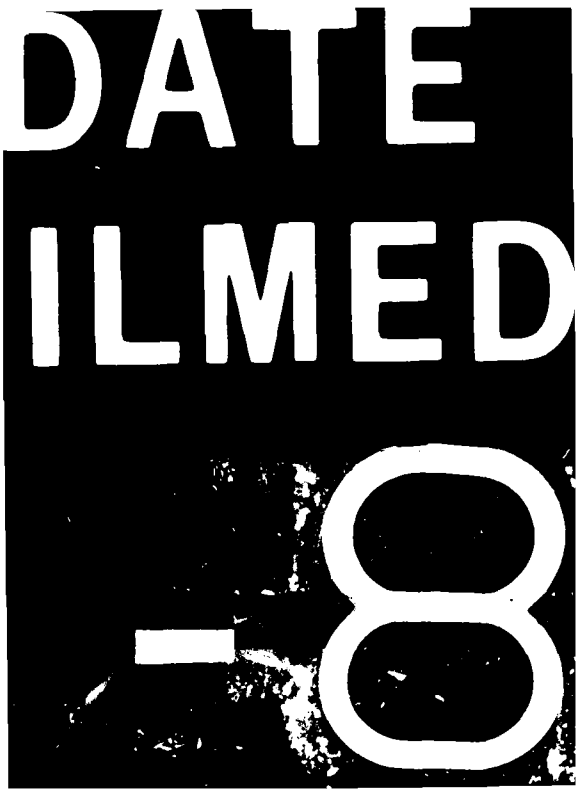
Commander
US Army Medical Bioengineering
Research and Development Laboratory
Fort Detrick, Frederick MD 21701

Commander
US Army Aeromedical Research Laboratory
Fort Rucker AL 36362

Commander
US Army Biomedical Laboratory
Aberdeen Proving Ground
Edgewood Arsenal MD 21010

Commander
Naval Medical Research Institute
National Naval Medical Center
Bethesda MD 20014

Commander
USAF School of Aerospace Medicine
Aerospace Medical Division
Brooks Air Force Base TX 78235


DATE
ILMED
-8